Clinically Severe Lactic Acidosis with Coma

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LACTIC ACIDOSIS of severe degree with coma is usually fatal. In about 95 per cent of reported cases reviewed by Tranquada[4] in which therapy could be interpreted, the patient died. Careful documentation and evaluation of all clinical, metabolic and therapeutic data of such cases is therefore vital to further understanding and more rational therapy.

Elevations of lactate can vary substantially in degree. However, in clinically severe cases excess lactate levels often are between 10 and 40 mM per liter. Increased concentrations can be found after muscle exercise or secondary to many clinical situations in which substantial general tissue anoxia exists. In these instances excess production is probably the primary factor. Altered metabolism in liver disease or decreased utilization secondary to drug alterations of normal or usual metabolic pathways can result in lactate excess. Often, probably the initial factor or factors, such as drug effect or altered liver function, lead to accumulation that can result in diverse direct and compensatory changes resulting in, among other manifestations, hypotension, anoxia and further increases of lactic acid, thereby in a matter of hours forming a vicious and often fatal cycle.

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The present case represented a state of severe clinical acidosis with associated derangement of blood chemical features in which a vigorous therapeutic program seemingly resulted in the successful outcome.

Report of a Case

A 52-year-old housewife was referred to the Woodland Memorial Hospital from an adjoining community on 22 November 1965. She had not been seen at this hospital previously. The patient had had known glycosuria dating back approximately 12 to 15 years and had been under supervision and active therapy for diabetes for five and a half years. At first, insulin had been given intramuscularly for control of diabetes, then oral medication for a year beginning approximately three years before admission, then reversion to 80 units of lente insulin a day about ten months before the present admission. The insulin dosage then was gradually lowered and after three months was discontinued. For seven months before admission the patient had been taking phenformin, (DBI), 25 mg four times a day.

The patient had cholecystectomy nine years before admission and she had been in hospital numerous times in the preceding four or five years for control of diabetes. Recently she had had no major disturbances to indicate clinical hypoglycemia nor was there a history of antecedent episodes of coma, of hepatic disease or, on careful questioning of friends and relatives, of alcohol intake.

Medications in addition to phenformin included hydrochlorothiazide (HydroDIURIL®) with potassium, taken once or twice a day and reserpine (Serpasil®) 2 mg three times a day. Antivert (meclizine dihydrochloride and nicotinic acid) one tablet once or twice a day had been used occasionally for dizziness but had not been used for sev-

eral weeks preceding admission. Trihexyphenidyl (Artane®) 2 mg four times a day, was used to control a mild tremor; and, in the past, meprobamate had been taken occasionally.

The patient had had hypertension of moderate degree for many years. During the 18 months before admission, particularly during the months she was taking phenformin, she had progressively lowered her weight from 250 to 198 pounds. Symptoms of diabetic neuropathy had been present for some months, and a bilateral coarse tremor described as of the paralysis agitans type had been fairly well controlled with Artane.® She took care of a family of three and was able to do the full general work of the home.

Thirty hours before admission the patient had had sudden onset of pain which she described as originating in both sides of the neck and going down into the chest with pressure-like precordial discomfort. The day preceding admission she had moderate shortness of breath and a low abdominal pain that radiated into the upper abdominal epigastric area, with nausea and vomiting and associated weakness on two occasions. Medications had been taken through the evening of the day before admission. Progressive weakness, anorexia and nausea continued on the day of admission, but she did not vomit again. The chest and neck pains had eased the morning of admission, but dull epigastric discomfort persisted. There had been no cough or evidence of respiratory infection and no chills, fever, sweating or diarrhea.

What with these multiple illnesses, the family had become fairly astute in clinical assessment and they judged the changes in the morning preceding admission to indicate substantial illness and progressive worsening. The referring physician therefore suggested immediate transfer by ambulance. However, the family elected to transport the patient themselves and thereby delayed admission for two and a half hours.

On physical examination the patient was observed to be tremendously large for her body build. She was lethargic and dazed, but with repeated stimuli she seemed oriented; and although she spoke slowly and in a dazed manner, her answers to questions were corroborated as being correct in content. Blood pressure was 90/55 mm of mercury. The pulse was 84 and regular. The skin was flushed and generally dry. Rectal temperature was 35.5°C (95.9°F), and not until 14 hours later did it reach 37°C (98.6°F). Tachypnea and hyperpnea and respirations of Kussmaul type were noted. The neck was supple. The pupils were medium sized and reacted sluggishly. The lungs were clear to auscultation. No abdominal tenderness or masses were defined and there were no signs of peritoneal irritation. The lower extremities were not edematous. Femoral pulses were moderately decreased in force and the pedal pulses were absent.

Shortly after admission the patient was in a very deep sleep, responding only slightly to stimulation; and subsequently she was stuporous and finally comatose. Laboratory data were as follows: Hemoglobin 14 gm per 100 ml of blood and packed cell volume was 42 per cent. Leukocytes numbered 31,000 per cu mm with neutrophils 84 per cent, non-segmented neutrophils 3 per cent, monocytes 3 per cent and lymphocytes 10 per cent. Blood urea nitrogen was 36 mg, blood sugar 167 mg and serum phosphorus 8.5 mg per 100 ml.

Table 1 shows initial and subsequent levels for other pertinent laboratory data, particularly as regards electrolyte and acid base balance. The serum examination for acetone at the time of admission showed no ketoacidosis and there was no acetonuria. Urinalysis showed a pH of 6.0, specific gravity 1.015, 1 plus sugar content, and 1 plus proteinuria. There were 8 to 10 erythrocytes per high power field and occasional granular casts. The serum glutamic oxaloacetic transaminase (SGOT) was 58 units, and the alpha-hydroxy

TABLE 1.—*Laboratory Data on Blood with Regard to Electrolyte and Acid Base Balance.*

Date	Time	pH	pCO_2 (mm Hg)	CO_2	Na	K	Cl	P	BUN	Glucose	Lactate	Pyruvate	Lactate Excess	Osmolarity
				(mEq/L)				(mg per 100 ml)			(mM per Liter)			
11-22	3:30 p.m.	6.83	25	9.9	137	4.6	104	8.5	36	167	24	0.23	19.5	307
	8:40 p.m.	6.99	37	....	.....	....	.....	....	....	.....	17	0.26	15.9	.....
11-23	7:00 a.m.	7.40	41	....	142	3.4	101	2.9	....	225	....	.. ....	.... ..	315
	2:00 p.m.	7.47	....	....	.....	....	.....	....	....	76	....	.. ....	.... ..	.....
11-24	6:30 a.m.	7.46	....	....	141	3.2	.....	....	25	266	....	.. ....	.... ..	303
11-26	6:30 a.m.	.. ....	....	....	134	3.5	.....	....	19	210	....	.. ....	.... ..	292
12-1	6:30 a.m.	.. ....	....	....	141	3.7	.....	....	....	175	....	.. ....	.... ..	.....

butyric dehydrogenase was 213 units. Cultures of stool, urine, blood and material swabbed from the throat did not grow pathogens. A week after admission the SGOT was 76 units with normal bilirubin and normal alkaline phosphatase. A serology test for syphilis was negative. Calcium phosphorus determinations at this time were within normal range, as were subsequent 17 ketosteroids and 17 ketogenic steroid levels. Urinary catechol levels were within normal range the eighth day after admission, and at that time the urine sodium and potassium excretion determinations over a 24 hour period also were normal.

The patient had been admitted at 2:15 p.m. and vigorous sodium bicarbonate therapy was begun at about 5:00 p.m. She was given sodium bicarbonate along with 1,000 ml of 5 per cent dextrose and saline solution at the beginning and then was also given sodium bicarbonate frequently by direct intravenous therapy. In the first seven hours 290 mEq of sodium bicarbonate was given intravenously and by the end of 14 hours a total of 404 mEq had been given. Shortly after intravenous bicarbonate therapy was begun, the first of two intravenous infusions of methylene blue was given—2.2 mg per kg of body weight at approximately 5:20 p.m. Mephentermine (Wyamine®) was given at first to maintain blood pressure, but as the pressure was subsequently maintained by the other fluid therapy, no other specific agent was used for this purpose after the first hour. Oxygen was administered by tent early. At 9:30 p.m. an additional intravenous infusion of methylene blue, 2.2 mg per kg of body weight, was given at a steady rate over the course of an hour.

The comatose state continued through approximately 6:30 p.m. and then progressive clearing ensued, the patient being considerably more alert by 10:00 p.m. She was at this time talking and asking questions, although she was confused as to time and place. At 9:15 p.m. the blood pressure was 160/90 mm of mercury and the pulse rate 120. Hyperpnea and warm dry skin continued.

At 6:45 the following morning moderate acetonuria was noted for the first time, but no glycosuria. It was felt that a phase of ketoacidosis was beginning and therapy was so directed. By noon that day, 22 hours after admission, the patient had 2 plus glycosuria and a trace of acetonuria. By evening, acetonuria and glycosuria had cleared. Blood sugar was 76 mg per 100 ml. Very small amounts of insulin were necessary therapeutically. X-ray films of the chest made early and subsequently showed no focal effusions or evidence of infiltration or congestion. An electrocardiogram was not specifically abnormal, but was compatible with a metabolic disturbance.

The patient steadily improved. At the time of discharge she was fully ambulatory with diabetes controlled with 25 units of insulin. The blood pressures remained in the range of 160/190 to 190/110 mm of mercury. Subsequent gastrointestinal roentgenographic studies showed no abnormality except minimal diverticulosis of the sigmoid colon and an electrocardiogram did not show myocardial infarction.

Discussion

The problem of a patient with clinically severe acidosis confirmed by immediately available laboratory studies showing a pH of 6.83 and a carbon dioxide content of 9.9 mEq per 100 ml of blood, and with no acetonuria or acetonemia demonstrable, should arouse suspicion of possible lactic acidosis among the other differential diagnostic considerations. Lactic acid determinations are often not readily available in many facilities. If early vigorous correction of the acidosis by administration of bicarbonate is to be followed by a possibly more definitive treatment such as intravenous infusion of methylene blue, it would be desirable to have some rapid test which would strongly suggest the acidosis was secondary to substantial lactate excess. Tranquada[4] noted a two- to three-fold elevation of serum phosphorus levels when the blood urea nitrogen is only moderately elevated in many instances of lactic acidosis. The phosphorus level of 8.5 in the present case confirmed the suspicion of probable lactate excess. The remaining serum of the specimens taken at 3:30 and 8:40 p.m. (See Table 1) was frozen and therapy was directed on a presumption of lactic acidosis. The lactate levels were subsequently determined by two methods, the colorimetric method described by Barker and Summersun (*Journal Biological Chemistry,* 138:535, 1941), and the enzymatic method of Loomis (*Journal of Laboratory and Clinical Medicine,* 57:966-969, June 1961).

In the present case survival from a usually fatal illness may have been owing to early vigorous bicarbonate therapy, to methylene blue treatment or to the combination of the two. Reported treatment in other cases with bicarbonate has usually

not been successful. It might be quite important, therefore, to make a presumptive diagnosis on the basis of clinical and laboratory findings of severe acidosis without ketosis and elevated phosphorus, and to begin treatment accordingly without immediate confirmation of elevated lactate levels, unless facilities for determining lactate content of the blood are at hand.

Daughaday and coworkers[2] have reported adequately documented cases of nonketotic acidosis in diabetic patients. The patients were not taking phenformin. Generally the response in those cases to therapy with sodium bicarbonate was rapid and good. The variability in the elevation of lactate and the clinical correlation with the degree of acidosis in coma has been apparent to many investigators.[3] The patient in the present case, who had a history of hypertension, had clinical symptoms of severe acidosis with rapid progression and apparent deterioration associated with hypotension. It was because of the clinical condition and a reduction of pH to 6.83 that the vigorous therapy was undertaken. Retrospectively one wonders if improvement might not have been equally good with large amounts of bicarbonate along with other supportive measures, without methylene blue. However, from review of the literature it is apparent that in cases in which there is derangement of the acid base balance and an associated clinical deterioration or considerably altered status sensorium, the patient usually dies. Moreover, in the present case, on suspicion that there might be a pharmacological anoxic derangement of the normal metabolic or oxidative pathways, bicarbonate was given early to correct the acidosis; and then methylene blue was added to provide an alternate oxidative system as had been outlined by Tranquada and coworkers.[5]

Perhaps the favorable outcome in the present case was owing to the early beginning of vigorous bicarbonate therapy, although Tranquada[6] and Bernier[1] reported early treatment without success. The arterial pH of 6.83 in the present case was among the lowest reported in similar cases, the lowest among cases in which there was so severe a clinical deterioration and the patient lived.

GENERIC AND TRADE NAMES OF DRUGS

Phenformin—*DBI.*
Hydrochlorothiazide—*Hydrodiuril.*
Reserpine—*Serpasil.*
Meclizine dihydrochloride and nicotinic acid—*Antivert.*
Trihexyphenidyl—*Artane.*
Methentermine—*Wyamine.*

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Disseminated Tuberculosis Of Bone

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DISSEMINATED BONE tuberculosis is not often reported. O'Malley and coworkers[13] reviewed the world literature and noted that although over 500 cases had been reported, only 60 had been carefully documented by strict pathologic and bacteriologic criteria. Reviewing 36,372 unselected admissions for tuberculosis, McTammany and coworkers[12] reported that osteoarticular tuberculosis was present in 3.8 per cent of patients, and that only 4.6 per cent of this latter group presented with multiple lesions of the skeletal system. Although statistically unsubstantiated at present, there appears to be a trend toward a decreasing incidence of skeletal tuberculosis, reflecting both the control of bovine tuberculosis in the United States and the development of effective anti-tuberculous agents.[6,11,12]

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